HUMAN ORGAN-ON-CHIP MODELS FOR PREDICTIVE SCREENING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of International Application No. PCT/US19/43722, filed Jul. 26, 2019, which claims priority to U.S. Provisional Application Ser. No. 62/711,221 filed Jul. 27, 2018, entitled "Integrated Modular Microphysiological System on a Chip," each of which are incorporated herein in their entireties by reference thereto.

GOVERNMENT FUNDING

[0002] This invention was made with government support under EB025765 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] The disclosed subject matter describes an integrated modular microphysiological system including two or more wells and a vascular network comprising at least one channel, and at least one endothelial barrier in fluid contact with the wells and the vascular network.

BACKGROUND

[0004] The current process of drug development is long, expensive, and inefficient largely due to the lack of predictive preclinical testing models. The development of new cancer therapeutics has one of the lowest success rates compared to other medical fields, with only 1 in 15 new drugs that have reached clinical trials receiving FDA approval. At the same time, some potentially effective therapeutic modalities may be eliminated in preclinical studies. While cancer remains a leading cause of morbidity and mortality worldwide, treatment options are limited by the low translational success of current preclinical testing models.

[0005] Cancer drugs, such as endostatin, have yielded promising results in mice, such as full tumor elimination when used alone, to subsequently show only minimal results in human patients. On the other hand, tamoxifen, a selective estrogen-receptor modulator, has been successfully used to treat breast cancer for years. However, if its predisposition to cause liver tumor in rats had been discovered in preclinical tests, the drug would have been eliminated during developmental testing. Other drugs have passed preclinical trials and then withdrawn, due to the side effects detected only during clinical trials or even after entering the market and being used by large numbers of patients. This is particularly true for cardiac side effects, as successful preclinical and clinical screening still allowed cardiotoxic drugs to enter the market. Rofecoxib, a COX-2 inhibitor used as an analgesic and anti-inflammatory drug, was approved by the FDA in 1999 and then removed from market in 2004 because of side effects not seen in preclinical and clinical trials. Unfortunately, by that time, the drug had already caused an estimated 140,000 heart attacks associated with 60,000 deaths.

[0006] Results like these illustrate the need for more predictive models of drug safety and efficacy, which would enable thorough testing of cardiac side effects. While regulatory changes have prevented drugs causing lethal arrhythmia from reaching the market, the current screening models are often oversensitive to proarrythymic side effects and result in elimination of numerous drugs. To date, as high as 60% of new drugs test positive for proarrhythmic events, based on assessing the rapid component of the delayed rectifier potassium current (IKr) for its blocking liability. The false positives are responsible for preventing the potentially lifesaving compounds from reaching the market.

[0007] What is needed is a preclinical model that could more accurately predict both the efficacy and the safety of new drugs in humans that could enable more reliable drugs to progress through the developmental pipeline. While the development of human induced pluripotent stem (iPS) cells provides a human cell source for preclinical testing, the relative immaturity and the lack of biological fidelity limit their use.

SUMMARY

[0008] The present disclosure is directed to an integrated modular microphysiological system on a chip.

[0009] The present disclosure provides a complex human-based integrated organ-on-a-chip system which can be used as a model during drug discovery, screening, and preclinical to clinical trials, specifically, by using an endothelial barrier the system enables the integration of multiple tissue types in a way that provides true separation to enable each tissue to be cultured in its specific culture media while still providing communication between tissues via a vascular network. The system can also provide a tool for researchers to investigate mechanisms underlying disease.

[0010] The present disclosure also provides a method and system for independently culturing multiple organ systems and connecting mature tissue cultures in a modular microphysiological system that overcomes many of the aforementioned limitations. Multiple tissue types can be derived from a single human induced pluripotent stem cell line and tissues are separated into individual compartments that eliminate the need for common culture media. Perfusion of a vascular medium, such as a blood substitute, through the entire system mimics the human circulatory system and allows for the introduction of drugs or circulating immune cells in a biomimetic manner. Moreover, the platform can be fabricated from a biocompatible, non-absorptive material and need not contain PDMS. This system can provide a customizable model of human physiological response and has the potential to facilitate more efficient and cost-effective drug development and drug screening

[0011] In some embodiments an integrated modular microphysiological system is provided which includes two or more chambers and a vascular network which includes at least one channel. Each well can be configured for culturing a tissue and includes a layer of endothelial cells which forms an endothelial barrier within the chamber. The endothelial barrier can be in fluid contact with at least one of the at least one channels in the vascular network. The endothelial barrier can also be in fluid contact with a fluid in the chamber.

[0012] In some embodiments, an integrated modular microphysiological system is provide which includes a vascular network and two or more chambers for culturing two or more tissues. Each chamber can include a layer of endothelial cells to form at least one endothelial barrier at the bottom of the chamber. The at least one endothelial barrier can be in fluid contact with at least one of the said at